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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
MARVICH, MARIA

ART UNIT	PAPER NUMBER
1636	6

DATE MAILED: 07/19/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/068,916	RITTER ET AL.	
	Examiner	Art Unit	
	Maria B. Marvich	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-17 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-17 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 11 February 2002 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 5 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Priority

Acknowledgment is made of applicant's claim for foreign priority based on an application filed in Germany on 6/9/2000. It is noted, however, that applicant has not filed a certified copy of the 100 28833.2 application as required by 35 U.S.C. 119(b) until such copy is filed with the application; the effective filing date of instant application is 01/30/02.

It is noted that this application appears to claim subject matter disclosed in prior copending Application No. PCT/DE01/02184 , filed 6/8/01. A reference to the prior application must be inserted as the first sentence of the specification of this application or in an application data sheet (37 CFR 1.76), if applicant intends to rely on the filing date of the prior application under 35 U.S.C. 119(e) or 120. See 37 CFR 1.78(a). Also, the current status of all nonprovisional parent applications referenced should be included.

If the application is a utility or plant application filed on or after November 29, 2000, any claim for priority must be made during the pendency of the application and within the later of four months from the actual filing date of the application or sixteen months from the filing date of the prior application. See 37 CFR 1.78(a)(2) and (a)(5). This time period is not extendable and a failure to submit the reference required by 35 U.S.C. 119(e) and/or 120, where applicable, within this time period is considered a waiver of any benefit of such prior application(s) under 35 U.S.C. 119(e), 120, 121 and365(c). A priority claim filed after the required time period may be accepted if it is accompanied by a grantable petition to accept an unintentionally delayed claim for priority under 35 U.S.C. 119(e), 120, 121 and 365(c). The petition must be accompanied by (1) a surcharge under 37 CFR 1.17(t), and (2) a statement that the entire delay between the date

the claim was due under 37 CFR 1.78(a)(2) or (a)(5) and the date the claim was filed was unintentional. The Commissioner may require additional information where there is a question whether the delay was unintentional. The petition should be directed to the Office of Petitions, Box DAC, Assistant Commissioner for Patents, Washington, DC 20231.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 3, 4 and 10 are rejected under 35 U.S.C. 102(b) as being anticipated by Georges et al. Recipient-specific cytotoxic T-lymphocytes were generated by bulk mixing of lymphocyte cultures between dog lymphocyte antigen haploidentical littermates (page 540, column 2, 3rd full paragraph). Cells were further restimulated with allogeneic irradiated peripheral blood mononuclear cells (page 540 column 1. last sentence through 541, column 2, line 1-2). Mixed lymphocyte cultures were retrovirally transduced with herpes simplex virus thymidine kinase gene, a gene often used therapeutically (page 540, column 2, 3rd paragraph).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-17 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the

art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation (*United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is required is not based on a single factor but is rather a conclusion reached by weighing many factors (See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter, 1986) and In *re Wands*, 8USPQ2d 1400 (Fed. Cir. 1988); these factors include the following:

1) Unpredictability of the art. This invention recites a gene-modified T cell and processes of generating said cells comprised of stimulation of a recipient T-cell followed or accompanied by transfection with a therapeutic gene. Further, the invention reads on prevention or treatment of transplant rejection in humans through the *in vivo* administration of *in vitro* genetically modified T cells. The only disclosed use of the compositions is for the prevention of graft rejection.

The invention provides for the *ex vivo* transfer of DNA into T-cells prior to their transfer into human patients. *Ex vivo* gene transfer is most commonly accomplished and is disclosed in the instant application utilizing retroviral vectors. However, other means of transfections into T-cells claimed in the invention such as liposome formulations constitute an unpredictable art due to their lack of efficacy. Several fundamental problems exist with *ex vivo* gene therapy. Often when cells are transduced back into the patient, sustained reliable expression is not maintained.

Additionally, the efficiency of transplantation of the infected cells is another challenge to the success of this therapy.

Many *in vitro* and animal models that are provided as evidence of success of treatment have not translated into successful treatment in humans. The *in vitro* assays with modified T cells generated according to the invention provide evidence that use of transgenic T cells expressing vIL-10 *in vitro* has promise. However, *in vitro* results have not always correlated well with *in vivo* clinical trial results in patients. In the case of transplant acceptance, "making it difficult to find an *in vitro* correlate of *in vivo* tolerance" (Waldmann, 1998). In reality, success of gene therapy of any condition in humans is extremely limited.

The unpredictability of using the claimed invention for use in humans is mitigated due to the lack of methods or processes disclosed in the specification. Many parameters must be addressed for *in vivo* use and yet there are no methods or means disclosed such as delivery methods for the introduction of the modified cells into humans, means of preparing the T-cells for *in vivo* applications, which genes and the safety of their use, biosafety issues of transfection protocols and efficiency of transgene expression. Prevention of diseases is an unpredictable art. In humans, transplants are usually established before therapy is offered. The specification does not adequately teach how to effectively predict for whom the prevention would be required.

2) State of the art. The state of transplant medicine art historically utilized compounds such as cyclosporin A, glucocorticoids and OKT3 to ensure transplantation by suppressing an immune response. However, these treatments require long-term exposure and often are associated with immunosuppression complications. Another means of suppressing immune responses though T-cell depletion was found to be limited in success in ensuring graft

acceptance. More recently, approaches to ensuring graft acceptance have focused on altering the graft versus host disease response. Targets have primarily been the altering or masking of the immune response of the donor cells. These are currently under much research.

Gene Therapy as proposed in the instant application is a highly unpredictable art. Limitations of T-cell delivery of therapeutic genes for human use include, the lack of efficiency of gene transfer to stem and primary cells, sustained tolerance to the gene modified T cells, prolonged survival of the genetically modified cells. Some regimens have observed a lack of sustained persistence of these cells (Greenberg et al, 2001). Much promise has been proposed for IL-10 claimed in invention also. However, IL-10 has been reported to under some circumstances act as an immune stimulant for T-cell mediated responses *in vivo* (Zeller, page 3684, column 2, line 1-3) depending on the dose (page 3890, column 1, line 1-5). Therefore, the state of art of gene-delivery was not high at the time of invention.

3) Number of working examples. The specification provides by way of working examples, generation of modified T cells expressing IL-4, IL-10, IL-12p40 using amphotrophic retroviral cells lines. The T cells are used in an experimental *in vitro* model to show decreased transplant rejection.

4) Amount of guidance provided by applicants. The specification provides as guidance for the delivery of therapeutic genes into T-cells use of a retroviral gene delivery cell line. Also mentioned is the use of lentivirus, AAV and CMV based viral delivery systems as well as liposome mediated gene transfer. Specifically, guidance is provided for generation of the retroviral packaging cell line that expresses IL-4, IL-10, IL-12p40. Additional guidance is provided for the preparation of T cells from a graft recipient and cells of the graft donor,

combining the mixed lymphocyte culture with the retroviral cell lines selection of G418 resistant cells.

The specification does not adequately teach how to effectively prevent transplant rejection or reach any therapeutic endpoint in humans. Several factors not considered in the specification include treatment intensity, accompanying immunosuppression drugs and schedule of treatment. This guidance provided by the applicants particularly does not provide for human patients with the potential for or actual need for prevention of transplant rejection. There is no exemplary method provided for clinical or pre-clinical use of the proposed invention.

5) Nature of invention. The invention recites the in vitro generation of genetically modified T cells. This invention requires a combination of molecular cloning, viral and cell culture techniques.

6) Level of skill in the art. The level of skill in the art covering this invention was not high at the time of invention. The development of was rapidly advancing in the field. But the field of gene therapy was just beginning to emerge including preclinical trials and animal models.

7) Scope of the invention. This invention has scope in that it recites a method for the prevention and treatment of by introduction of.

In view of predictability of the art to which the invention pertains and the lack of established clinical protocols to predict for whom the therapies would be required: undue experimentation would be required to practice the claimed methods with reasonable expectation of success, absent a specific and detailed description in Applicant's for how to reasonably determine how to use the claimed cellular compositions.

Given the above analysis of the factors which the courts have determined are critical in determining whether a claimed invention is enabled, it must be concluded that the skilled artisan would have had to have conducted undue experimentation and excessive experimentation in order to practice the claimed invention.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria B Marvich, PhD whose telephone number is (703) 605-1207. The examiner can normally be reached on M-F (6:30-3:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucell, PhD can be reached on (703) 305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 305-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the patent analyst, Kay Pinkney, whose telephone number is (703) 305-3553.

Maria B Marvich, PhD
Examiner
Art Unit 1636

July 15, 2002

DAVID GUZO
PRIMARY EXAMINER